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Proton pump inhibitors are associated with a high rate of serious infections in veterans with decompensated cirrhosis

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SUMMARY

Background and Aims—To estimate the extent which proton pump inhibitors (PPIs) increase the rate of infections among patients with decompensated cirrhosis.

Methods—We conducted a retrospective propensity-matched new user design using US Veterans Health Administration data. Only decompensated cirrhotic patients from 2001–2009 were included. New PPI users after decompensation (n=1,268) were 1:1 matched to those who did not initiate gastric acid suppression. Serious infections, defined as infections associated with a hospitalization, were the outcomes. These were separated into acid suppression-related (SBP, bacteremia, *C.difficile* and pneumonia) and non-acid suppression-related. Time varying Cox models were used to estimate adjusted hazard ratios (HR) and 95% confidence intervals (CI) of serious infections. Parallel analyses were conducted with H2 receptor antagonists(H2RA).

Results—More than half of persons with decompensated cirrhosis were new users of gastric acid suppressants, with most using PPIs (45.6%) compared to H2RAs (5.9%). In the PPI propensity matched analysis, 25.3% developed serious infections and 25.9% developed serious infections in the H2RA analysis. PPI users developed serious infections faster than non-gastric acid suppression users (adjusted HR: 1.66; 95% CI:1.31–2.12). For acid suppression related serious infections, PPI users developed the outcome at a rate 1.75 times faster than non-users (95% CI: 1.32 to 2.34). The H2RA findings were not statistically significant (HR serious infections: 1.59; 95% CI: 0.80–3.18; HR acid suppression related infections: 0.92; 95% CI: 0.31–2.73).

Conclusions—Among patients with decompensated cirrhosis, PPIs but not H2RAs increase the rate of serious infections.

Keywords

Acid suppression; mortality; end-stage liver disease; H2 receptor antagonists; spontaneous bacterial peritonitis

INTRODUCTION

Infections in cirrhosis, especially those associated with intestinal bacterial overgrowth and translocation such as spontaneous bacterial peritonitis (SBP), are responsible for a substantial cost of care and can increase mortality up to four-fold (1–4). These infections can impact patients directly by causing death or indirectly by precipitating hepatic encephalopathy and renal failure or reducing liver transplant eligibility(4, 5). The leading pathogenic mechanism behind these infections in cirrhosis is small intestinal bacterial overgrowth (SIBO) leading to bacterial translocation, a process that is enhanced by acid suppression(5–7). Efforts to reduce this tremendous burden in cirrhosis by potentially reducing the bacterial translocation and overgrowth are needed(8).

The association of acid-suppressive agents, such as proton pump inhibitors (PPI), with infections such as pneumonia, *C. difficile* and infectious gastroenteritis has been studied extensively in non-cirrhotic patients(9–13). The mechanism cited is related to the SIBO and a direct immunosuppressive effect making patients prone to bacterial translocation(14, 15). PPI use is prevalent in the cirrhotic as well as non-cirrhotic population(16–19). There is also a growing body of evidence that PPIs are related to serious infections related to SIBO in cirrhosis such as SBP and *C. difficile*(20–23). However, these were single-center studies with limited sample sizes.

Our *aim* was to estimate the extent which PPIs increase the rate of serious infections among decompensated cirrhotic patients in a national Veterans Health Administration(VHA) database. The *a priori* hypothesis was that PPI use is associated with a higher rate of serious infections, especially those related to acid-suppression, in patients with decompensated cirrhosis.

METHODS

The McGuire VA Medical Center Institutional Review Board approved this protocol.

Design

We conducted a new-user cohort study among US veterans. Alcoholic liver disease and cirrhosis are epidemic in the US Veteran population(24). New use of gastric acid suppressant use was defined on the basis of pharmacy information. The new-user design eliminates prevalent use bias and provides better control of confounding(25). The rate of serious infections associated with PPI monotherapy and H2 receptor antagonists (H2RA) monotherapy was compared with no use of gastric acid suppressants. Propensity-matching was used to create a sample of patients who are similar on all potential confounders except the exposure variable of interest (26, 27).

Data Sources

The national shared electronic medical record system of the United States Veterans Health Administration (VHA) provided a data source suitable to evaluate this clinically important question. The VHA's Austin Information Technology Center (AITC) database contains information on millions of veterans throughout the country that can be linked to its Pharmacy Benefits Management (PBM) database containing information on medication use and frequency. All information is prospectively collected in these databases and is broadly representative of the US veteran population. A retrospective cohort study using the VHA AITC database from fiscal year 2001 through 2009 and the PBM database was performed. Baseline patient characteristics were obtained from the VA Decision Support System(28) and outpatient medical care datasets(29). This database does not include details of physical

examinations, non-coded events in the patient's history or laboratory values, therefore cirrhosis severity assessment and indications for therapies are not available.

Study Population

We identified 123,036 patients with a primary or secondary diagnosis coded as ICD-9-CM 571.2 (alcoholic cirrhosis of the liver), 571.5 (cirrhosis without mention of alcohol), 571.6 (Biliary cirrhosis) in the AITC. In the VA administrative data, these diagnostic codes are highly predictive of the presence of these conditions in medical records and can be reliably used for research(30). Then, we applied inclusion criteria as indicators that patients received care through the VA regularly. First, at least one year of follow-up data post-the initial hospitalization for cirrhosis was needed. Second, patients had to have at least two visits in the VA system. Third, patients had to have evidence of VA Pharmacy activity (at least one prescription). Among this group, we identified patients with decompensated disease. Decompensation was defined as presence of one of the following validated codes [hepatic encephalopathy (572.2), hepatorenal syndrome (572.4), spontaneous bacterial peritonitis (567.23), ascites (789.5) or variceal bleeding (456.0, 456.2)](31, 32). Patients were included if there was no evidence of a hospitalization for an infection in the six months before date of decompensation. The sample consisted of 7,299 patients who met these eligibility criteria.

From this group of eligible patients, we defined three patient cohorts who were new users (the remainder were already on these medications): 1) patients initiating PPI monotherapy (n=1,905); 2) patient initiating H2RA monotherapy (n=248); and 3) patients without any indication of gastric acid suppressant use (n=2,028). The date of the first filling was considered the index date for the former two patient cohorts. The index date for persons who did not user gastric acid suppressants was defined by the index date of the propensity matched PPI or H2RA users. That is, the number of days from cirrhosis diagnosis to index date of PPI or H2RA use was added to the date of cirrhosis diagnosis for the propensity-matched non-user. This method increased comparability with respect to the person time experience given the natural course of disease.

Infection Outcomes

There were two primary outcomes: time to first serious infection and time to first serious acid suppression-related infection. Serious infections were defined as those coded during an inpatient stay. Inpatient infections were defined as ICD-9 codes for: (a) Skin infection (including cellulitis):680–686, (b) lower respiratory infections (480–487), (c) SBP: 567.23, (d) urinary and kidney infections: 590.x, (e) *Clostridium difficile* (*C. difficile*): 008.45, (f) Infectious gastroenteritis:0090, (g) Sepsis and bacteremia (in the absence of a primary infection) including the following: (i) Bacteremia: 790.7 and (ii) Septicemia : 038.x. Previous work suggests that bacterial infections in the VA system are coded accurately(33). To further validate these and additional codes, we identified 128 cirrhotic patients in 2011 who were admitted as an inpatient to the Richmond VA Medical Center with any of the infections listed above. The charts were then reviewed by an MD (J.B.) to evaluate the appropriateness of the coding to the clinical situation. These diagnostic codes are highly predictive of the presence of these conditions in medical records as the positive predicted values were 93% for *C. difficile* infection, 100% for SBP, 93% for skin infections, 91% for pneumonia, 100% for septicemia, 92% for bacteremia and 94% overall.

The second outcome, acid suppression-related infections, was determined based on literature review: pneumonia, SBP, sepsis and spontaneous bacteremia (in decompensated cirrhosis are likely due to bacterial translocation if no specific organ/vascular entity is the source), infectious gastroenteritis and *C. difficile* (11, 34–36). For each outcome of interest, we

calculated person-time as time from index date (date of first PPI or for non-PPI users the matched index date) to date of event or the censored date (death or loss to follow-up date).

Exposure Assessment

We used the PBM database to identify exposure to gastric acid suppressants.(37) This database includes details of inpatient and outpatient medication use, including name of medication, doses, fill dates, quantity dispensed, and days' supply. While our initial motivation for conducting the research was focused on PPI use, we also evaluated the extent to which H2RA use was associated with serious infections as both classes reduce gastric acid. We hypothesized that there would be no relation between H2RAs and serious infections. Exposure was defined dichotomously as mono-therapy or no receipt of each category during each 30 day window from the index date. The thirty day window was selected as typically days of therapy on VA prescription claims for these medications were not less than 30 days. PPI use included omeprazole, esomeprazole, lansoprazole, rabeprazole, dexlansoprazole, and pantoprazole. H2RAs were studied separately to understand the specific contribution of degree of acid suppression. We required users to have received at least a 30 pill regimen.

Potential Confounders

We considered the following to be potential confounders because they have been known to be independent risk factors for infection: alcoholic etiology, severity of co-morbid conditions and concurrent medications.(38) Studies have shown a potential protective effect of non-selective beta-blockers (NSBB) on SBP but not in patients with refractory ascites. (39, 40) Rifaximin, which in the VHA system is only used for patients intolerant of lactulose, has been shown to protect against infections, especially *C. difficile*.(41) Alcoholic cirrhosis was defined using ICD9 Code 571.2. The Charlson comorbidity index was calculated using an ICD-9 search algorithm and was based on data from the year after first cirrhosis diagnosis.(42) Data on the co-morbid conditions come from the VHA outpatient and inpatient treatment files.(29) We also created a variable to capture the number of outpatient visits in the previous year. We initially considered the following concomitant medications as potential confounders, but ruled them out for further consideration. These included: corticosteroids, antiparkinson drugs, barbiturates, anxiolytics, antipsychotics, and opiates.

Statistical Analysis

We compared the distributions of socio-demographic and clinical characteristics of participants who were new PPI users, new H2RA users, and non-gastric acid suppressant users. To improve the balance of potential confounders across the exposure categories (PPI, H2RA, nonuse), we conducted propensity score analyses.(26, 27) The propensity score technique attempts to create a sample of patients who are similar on all potential confounders except the exposure variable of interest (in this case PPIs or H2RAs). To create the sample of PPI users matched to non-gastric acid suppressant users, we first created a predicted probability for treatment for each person. The predicted probability was estimated from a logistic regression model which included all risk factors for the serious infections. The propensity score models yielded C statistics suggesting good overlap. The new PPI users were matched to non-gastric acid suppressant users with a 1:1 ratio using the greedy algorithm method, which reduces matched-pair bias caused by incomplete matching.(43) This method improves inexact matching by making best matches first and then taking the next best matches, in a hierarchical sequence, until no more matches can be made. We used the same strategy to identify one gastric acid suppressant non-user for each H2RA new user. Despite the use of the greedy algorithm, we were unable to match 537 PPI new users to non-users and 49 H2RA new users to non-users; these are usually subjects with propensity scores

at the tail ends and including them would decrease the internal validity of the adjustment for the propensity matched sample. Visual inspection of the distributions of confounders across the exposure groups was conducted to evaluate the adequacy of the propensity score matching with respect to creating balance on measured confounders. If greater than 5% absolute difference in a potential confounder was observed across the gastric acid suppressant category, the variable would also be considered as a covariate in future analyses.

Using the propensity matched sample, we conducted several analyses. First, we calculated the crude incidence rates (per 1,000 person years) to provide descriptive rates in each population for the primary outcome (all serious infections) and the secondary outcome (acid suppression-related infections). Second, we developed four separate Cox models (PPI and H2RA separately; primary and secondary outcomes) to estimate crude hazard ratios. We developed two separate Cox regression models for PPI and H2RA separately: 1) to estimate the association between PPI (or H2RA) use and incidence rate of all serious infections; and 2) to estimate the effect of PPI (or H2RA) use on rate of acid-suppression-related infections. Although these Cox models included only a term for PPI use (or H2RA use), the propensity score matching adequately controlled for the measured confounders which achieved balance in the matching process. Despite the tight control for prevalent bias (through the new user design) and confounding (through the propensity matching), we were concerned about the time-varying nature of gastric acid suppressant drug use. Previously, we have shown the importance of considering time-varying drug exposures because the reliance on time-fixed methods may introduce bias.⁽⁴⁴⁾ Therefore, we estimated Cox models including time varying PPI use (or H2RA use), as well as other potential confounders. We used a 90 day window for the time varying component as the mode days of therapy for VA prescriptions for gastric acid suppressants was 90 days. The models produced hazard rate ratios and 95% confidence intervals. We confirmed the assumption of proportionality by visually inspecting the cumulative hazard function.

RESULTS

More than half of persons with decompensated cirrhosis were new users of gastric acid suppressants, with most using PPIs (45.6%) compared to H2RAs (5.9%). The majority of patients in the new PPI user group were on omeprazole (73%). The rest were on rabeprazole (23%), lansoprazole (2%), or pantoprazole (1%). Table 1 shows the distribution of socio-demographic and clinical characteristics by gastric acid suppressant use. The vast majority of patients with decompensated cirrhosis in the VA were men, and this did not vary by gastric acid suppressant use. Age and known race/ethnicity were also comparably distributed, although the proportion of missing data in the latter variable was very high. Cirrhosis etiology was commonly alcoholic and slightly more so among H2RA new users (49.6% H2RA versus 43.8% PPI users and 44.3% non-users). Hepatitis C infection was common with 52.4% of PPI new users and 46.0% of H2RA users and 46.3% non-users infected. The distribution of concomitant medications were similar between groups for antibiotics (and rare) and non-selective beta blockers (~12–14%). While rifaximin use was relatively low, it was slightly more prevalent among PPI users than non-users (6.8% PPI; 1.6% H2RA; 2.4% in non-users); this was equalized in the matched samples. The PPI and H2RA users had a greater proportion of people with at least 5 comorbid conditions relative to the non-users (PPI: 41.7%; H2RA: 41.9%; non-user: 31.1%). The majority of the events that led to the inclusion of patients as decompensated cirrhosis were ascites (73%), followed by hepatic encephalopathy (18%), variceal bleeding (8%), hepato-renal syndrome (1%); only 9 patients had SBP as their primary decompensating event.

Table 2 also shows the distribution of the potential confounders in the propensity-matched sample. The distributions of the potential confounders of the propensity-matched sample

appear well-balanced. Relative to the matched non-users (32.1%), PPI users had 5 or more comorbid conditions (41.2%). Similar imbalance was observed between H2RA users (41.7%) and non-users (34.7%).

Table 3 shows the association between gastric acid suppressant drug use and serious infections stratified by PPI and H2RA use. Among the propensity matched PPI cohort, 25.3% developed serious infections. Acid suppression associated infections were common (17.7%). Among the PPI users, acid suppression-related infections formed the bulk (75%) of all infections whereas among non-gastric acid suppressant users 64% of serious infections were acid-suppression related. Among the propensity matched H2RA cohort, 25.9% developed serious infections with 15% deemed acid suppressant-related. Although the bulk of serious infections in H2RA users were also acid suppression-related infections (64.7%) among non-users in this cohort 51.9% were acid suppressant-related infections. There was no significant difference in the patterns of infection occurrence based on the initial decompensating event between the PPI and non-PPI groups. Leading serious infections were SBP/peritonitis (30%) pneumonia (25%), skin infections (23%), spontaneous bacteremia and septicemia (16%), *C. difficile* (5%) and UTI (1%). During the study period, liver transplant was uncommon.

In the propensity matched sample for PPI users, there was no association between PPI use and the rate of serious infections (crude propensity-matched hazard ratio (HR): 1.08; 95% confidence interval (CI:) 0.90 to 1.31). However, PPI users tended to develop serious acid-suppression related infections at a rate higher than non-gastric acid suppressant users, although the confidence interval included unity (crude HR: 1.22; 95% CI: 0.97 to 1.52). As these estimates of effect are still prone to bias owing to the time varying nature of PPI use, we estimated the effect of PPI use on serious infections and acid-suppression related infections accounting for time varying PPI use. For serious infections, PPI users developed the outcome at a rate 1.66 times that of non-users (95% CI: 1.31 to 2.12). For acid suppression related serious infections, PPI users developed the outcome at a rate 1.75 times faster than non-users (95% CI: 1.32 to 2.34).

In the propensity matched H2RA analysis, no evidence of an association between H2RA use and infections was observed based on the crude analyses. While the analyses adjusting for time varying H2RA use revealed a hazard rate of 1.59 for H2RA use on all serious infections, the confidence interval was quite wide (95% CI: 0.80 and 3.18). No association between H2RA use and acid suppression associated infections was noted (adjusted HR: 0.92; 95% CI: 0.31 to 2.73).

DISCUSSION

We found PPI initiation to be prevalent among patients with decompensated cirrhosis. Further, we documented that the initiation of PPI therapy accelerates the rate of infections associated with hospitalization, especially those related to intestinal bacterial overgrowth and translocation, in decompensated cirrhotic patients. We also found that use of H2-receptor antagonists do not appear to accelerate the rate of these infections in decompensated cirrhosis, although our sample size was limited and could have explained the negative findings.

Infections are one of the leading causes of mortality in cirrhosis, most of which have a presumed gut bacterial origin(5). The effect of PPIs has been studied in case series in cirrhotic patients showing that their use was associated with a significantly higher risk of gut-based infections such as SBP and *C. difficile*(20–22). However, those studies were small in sample size and were unable to explore the time varying nature of PPI use. Previous

methodological research in pharmaco-epidemiology point to the bias introduced with treating drug exposures as fixed effects(44). Therefore the results need to be expanded in a larger pool of patients who would otherwise be predisposed to develop infections. The AITC and PBM databases represent a large cross-section of veterans treated in the US that can be used to answer clinically relevant questions.

In our study, we chose to use decompensated cirrhotic patients defined stringently according to previously used ICD-9 criteria in which the mode of initial decompensation did not influence the risk of infections. The AITC and PBM databases do not include laboratory variables permitting adjustment for cirrhosis severity. Nevertheless, our findings are likely robust owing to several design features. First, we matched the time period of observation from the date of decompensation for gastric acid suppressant users to non-users. In doing so, we have likely created comparability in the natural history. Second, we conducted a propensity matched analysis which included key confounders, as well as emerging risk factors for infections.(39) By matching via the greedy algorithm, our analyses included tight control for a variety of potential confounders (age, race, charlson score, alcoholic etiology, year of entry, non-selective beta-blockers, rifaximin, antibiotics, number of outpatient and inpatient visits in last year) which were shown to have balance across the gastric acid suppressant categories. Third, the factors we adjusted for are likely highly correlated to Child and MELD scores and are related to the decompensating events. Fourth, we included analyses of H2RAs as a counterfactual. Given the similarities in the distributions among H2RA and PPI users, it is highly unlikely that the PPI analyses would experience residual confounding by disease severity, but not the H2RA analyses. Lastly, we implemented a new user design which also provides better control owing to prevalent use bias, which means the biases owing to relative length of the PPI or H2RA use would be removed. Given these design considerations, we believe that our findings are robust.

Our study specifically concentrated on decompensated cirrhotic patients who were first initiated on gastric acid suppression therapy (PPI or H2RA) *after* they developed decompensation defined by the complications of cirrhosis such as variceal bleeding, ascites or hepatic encephalopathy. This method ensured that the specific duration of PPI use was available for study as well as the refills and total dose during the follow-up period. It is also the appropriate method to eliminate prevalent use bias. Doing so however, excluded patients with decompensated cirrhosis who had been on long-term PPI therapy *before* the decompensating event. This design therefore biased our results towards only showing an extreme effect of PPI use on the risk of infections; despite these restrictions, we were able to find that new PPI therapy significantly reduced the time to all infections and especially, time to gastric acid suppression-related infections.

To understand the extent to which PPIs as a class rather than simple acid suppression were associated with infections, we conducted a parallel study using identical methods on H2RA new users. We believed that if the mechanism was entirely through gastric acid suppression, we would find a lessened effect or no effect among H2RA users. Further, this analysis helped evaluate the extent to which the findings may have been due to confounding by indication. Indeed, we found no specific effect of H2RAs on infection risk. This may be a testament to the specificity of PPIs as harbinger of infections in cirrhosis either due to a class effect or due to a higher potency of acid suppression. A key strength of this paper was the study of time-varying on the days to infection rather than simply dividing patient groups into users and non-users. This also accounted for the days that the patients were not on PPI s. Indeed, we found that estimates of effect derived from the time-varying analyses were significantly higher than those created by fixed use of PPIs at study initiation.

The mechanisms behind the predisposition towards infections in cirrhotic patients initiated on PPI are unclear. Studies have shown the appearance of SIBO after PPI therapy, to which cirrhotic patients are predisposed to given the abnormal intestinal motility and neuro-hormonal imbalance in the gut milieu.(15) There is also evidence that PPIs have depressive effects on neutrophil action and innate immunity, adding a direct anti-inflammatory component to this predisposition.(14) The presence of SIBO in cirrhosis is associated with peripheral bacterial DNA isolation signifying intestinal bacterial translocation, which worsens in decompensated patients.(7, 45) Interestingly recent reports have shown that acid suppression can alter microbial flora even in the lower gastrointestinal tract.(10, 46) The finding that PPI therapy reduces the time to infections may be due to this effect but mechanistic studies need to be performed in order to confirm this. However, it is clear that in this dataset, the co-administration of other studied drugs did not change the effect of PPI on rate of infections in cirrhosis. This comparatively rapid development of serious infections, especially in decompensated cirrhotics, can be significant in determining prognosis as determined by eligibility for liver transplantation and can modulate further decompensating events(4). In our group indeed we found that patients who were newly initiated on PPIs after decompensation also had a faster progression to death and liver transplant, which is in essence organ death.

Although this study sample is one of the largest in which PPI therapy has been studied in cirrhosis, there are several caveats. Due to the lack of cirrhosis severity parameters, it may be possible that the patients started on PPI could have a worse cirrhosis severity and hence a higher infection, death and transplant rate. To mitigate this, we implemented a variety of robust techniques to ensure that they were comparable in the matched sample, but cannot rule out residual confounding entirely in a non-experimental study. We used ICD-9 codes to define the population, as well as to define the outcomes of interest. However, the positive predictive values for these outcomes in VHA settings are quite high indicating their usefulness for research purposes. We also excluded those followed for less than a year, meaning that if a patient died of sepsis within the first year, they would not be counted. This was done to ensure adequate follow-up in the VHA system. Although the study also could not account for the reason for PPI initiation, parallel analyses of H2RA helped rule out confounding by indication as an explanation of these findings. It may be that nonusers of gastric acid suppressants filled prescriptions outside of the VA system as veterans may be eligible for more than one health care system. In 2003, more than 50% of VA enrollees had Medicare coverage, including 22% of those under age 65.(47) We reduced this source of bias by excluding Veterans who had not received at least one medication through the VA. Regardless, if present, this source of bias would have only attenuated the estimate of effect reported in our study.

We conclude that Veterans with decompensated cirrhosis who were started on PPI therapy after decompensation had a significantly higher risk of developing serious infections compared to those who were not initiated on gastric acid suppression. This increase in risk occurs in a time-varying fashion and is not explained by confounding by concomitant drug use, comorbid conditions, or age. Since patients with decompensated cirrhosis remain at a high risk of serious infections, clinicians should re-evaluate the reason for prescribing PPI and wherever possible, replace their acid suppressive needs with H2RAs. Further studies are required to prospectively analyze the value of PPI withdrawal in patients with decompensated cirrhosis.

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1. Authors declaration of personal interests

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Table 1

Comparison of Characteristics By Gastric Acid Suppressant Use

	Total Sample (N=4,181)		
	PPI Only Users (N=1,905)	H2RA Only Users (N=248)	Gastro Suppressant Non-Users (N=2,028)
Age (years)			
<55	46.6	52.0	40.9
55–64	39.2	33.9	39.8
65–74	10.4	7.7	11.7
75+	3.8	6.5	7.5
Race/Ethnicity			
White	38.1	41.5	36.4
Black	5.4	8.5	5.6
Hispanic	3.8	6.0	5.3
Other	0.4	0.0	0.7
Unknown	52.3	44.0	52.0
Women	1.3	0.8	1.5
Drug Use at Baseline			
Non-Selective Beta Blocker	13.9	12.1	14.2
Rifaximin	6.8	1.6	2.4
Antibiotics	1.5	0.8	2.0
Outpatient Visits in Past Year (median, IQR)	7 (14)	5 (13)	8 (16)
Charlson Score			
1–2	28.1	31.5	39.2
3–4	30.2	26.6	29.8
5+	41.7	41.9	31.1
Alcohol-Related Cirrhosis	43.8	49.6	44.3
Hepatitis C	52.4	46.0	46.3

All values are percentages unless otherwise indicated.

Table 2

Comparison of Characteristics Between Propensity Matched Samples

	PPI Matched Sample (N=2,536)		H2RA Matched Sample (N=398)	
	PPI Only Users (N=1,268)	Non-Users (N=1,268)	H2RA Only Users (N=199)	Non-Users (N=199)
Age (years)				
<55	42.0	47.2	51.8	51.8
55–64	42.3	39.0	33.7	34.2
65–74	11.8	9.0	8.5	8.5
75+	3.9	4.7	6.0	5.5
Race/Ethnicity				
White	35.8	39.0	38.7	39.2
Black	5.8	5.4	10.1	9.5
Hispanic	4.7	3.9	5.0	5.0
Other	0.6	0.5	0.0	0.0
Unknown	53.1	51.3	46.2	46.2
Women	1.1	1.3	1.0	1.5
Drug Use at Baseline				
Non-Selective Beta Blocker	12.4	14.6	10.6	13.1
Rifaximin	2.8	2.8	1.5	2.5
Antibiotics	1.7	1.7	1.0	1.5
Outpatient Visits in Past Year (median, IQR)	6 (13)	8 (15)	5 (13)	7 (14)
Charlson Score				
1–2	26.5	37.1	31.7	39.2
3–4	32.3	30.8	26.6	26.1
5+	41.2	32.1	41.7	34.7
Alcohol-Related Cirrhosis	46.8	43.9	51.3	51.3
Hepatitis C	49.5	49.9	44.2	45.2

All values are percentages unless otherwise indicated.

Table 3
Effect of new user of PPIs and H2RAs on Infections Among Propensity Matched Samples

PPI Propensity Matched Sample (N=2,536)	Number of Cases	Person Years	Incidence Rate per 1,000 Person Years	Crude Hazard Ratio [*]	Adjusted Hazard Ratio ^{**}
All Infections					
PPI users	320	474	675		
Gastric suppressant non-users	321	459	700	1.08 (0.90–1.31)	1.66 (1.31–2.12)
Acid Suppression-Related Infections					
PPI users	241	346	696		
Gastric suppressant non-users	207	290	714	1.22 (0.97–1.52)	1.75 (1.32–2.34)
H2RA Propensity Matched Sample (N=398)					
All Infections					
H2RA users	51	63	814		
Gastric suppressant non-users	52	83	628	1.09 (0.68–1.73)	1.59 (0.80–3.18)
Acid Suppression-Related Infections					
H2RA users	33	39	844		
Gastric suppressant non-users	27	37	730	1.10 (0.60–2.02)	0.92 (0.31–2.73)

* Crude hazard ratios come from unadjusted Cox proportional hazard models with baseline new use of PPI or H2RA.

** Adjusted hazard ratios come from Cox proportional hazard models with time-varying PPI or H2RA use adjusted for age, source fiscal year, Charlson comorbidity score, alcoholic etiology, hepatitis C, baseline non-selective beta blocker use, number of visits, and number of hospitalizations.